Group A, B, and D, 200 µg for Group C) and were monitored for 144 hours (Group A, B, and C) or 72 hours (Group D). PK samples were analyzed by liquid chromatography coupled to tandem mass spectrometry. PK parameters of selexipag and ACT-333679 were explored using ratios of geometric means and their 90% CIs.
Results: PK results (geometric mean (95% CI)) are presented in the **table** below:

	Group A		Group B		Group D	
Parameter	Selexipag	ACT-333679	Selexipag	ACT-333679	Selexipag	ACT-333679
Cmax1 [ng/mL]	3.9 (2.8–5.3)	4.5 (3.1–6.7)	5.4 (3.9–7.3)	5.3 (4.6–6.0)	1.9 (1.5–2.4)	3.8 (3.0–5.0)
tmax2 [h]	1.0 (1.0–4.0)	5.0 (3.0–6.0)	2.0 (1.0–6.0)	6.0 (4.0–7.0)	1.0 (1.0–2.0)	4.0 (4.0–6.0)
t1/23 [h]	1.6 (1.3–2.1)	6.5 (4.9–8.6)	2.2 (1.6–3.0)	15.9 (10.1–25.0)	1.1 (0.8–1.4)	12.6 (9.1–17.5)
AUC0-∞4 [ng*h/mL]	10.9 (8.6–13.8)	29.6 (20.6–42.6)	23.5 (17.0–32.4)	56.1 (42.8–73.5)	5.3 (4.5–6.2)	25.3 (21.9–29.3)

[1]peak concentration; [2]time to reach Cmax, median (range); [3]terminal half-life, [4]exposure from 0 to ∞.

The free fraction of both compounds in plasma increased only in Group B (30%). Group C PK data are not included here (2 subjects only). Selexipag 400 µg was generally well tolerated in all groups. Ten subjects reported 14 adverse events: 4, 6, 2, and 2 in Group A, B, C, and D, respectively. One serious adverse event (hepatic encephalopathy) occurred in Group C, in the context of urinary infection and previous history of encephalopathy. No clinically relevant changes in clinical laboratory variables and electrocardiograms were observed.
Conclusion: Selexipag exposure increased in subjects with mild or moderate liver impairment compared with healthy subjects whereas exposure to ACT-333679 remained unchanged in subjects with mild liver impairment and doubled in subjects with moderate liver impairment. No conclusion could be drawn for severe liver impairment.
Disclosure of Interest: None declared.

PP195—VORICONAZOLE ADJUSTMENT FROM TWICE TO THREE TIMES DAILY IN CYSTIC FIBROSIS LUNG TRANSPLANT PATIENTS

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Introduction: Azole antifungal drugs display a nonlinear pharmacokinetic profile and present pharmacokinetics/pharmacodynamic relationships that is the reason why therapeutic drug monitoring is highly recommended. In time, we observed that cystic fibrosis lung transplant patients show an extensive metabolism and that dose escalation, without reducing time between dose intervals, cannot lead to reach optimal blood level. The objective of this work is to evaluate the administration of voriconazole 3 times daily to reach the therapeutic range (1–4.5 mg/L) in this population.
Patients (or Materials) and Methods: A retrospective study was carried out on cystic fibrosis lung transplant patients. Inclusion criteria were as follow: intravenous administration of voriconazole twice daily with a trough concentration <0.5 mg/L, and then dose adjustment from twice to 3 times daily. Trough concentration was compared before and after dose adjustment. A validated high-pressure liquid-chromatography tandem mass spectrometry assay was used to determine voriconazole concentrations
Results: Seven cystic fibrosis patients have been included (4 males, 3 females)

	n	7
	age (years)	24.7 (5.44) [21–32]
	weight (kg)	48,8 ± 4,95 [44–56)]
	time posttransplant (days)	22,8 ± 27,13 [8.5–83.5]
	Before dose adjustment	After dose adjustment
Trough concentration (mg/L)	0.25 (0.15) [0.03–0.52]	2.26 (1.10) [0.68–4]
Voriconazole dose (mg/kg)	6,47±2,12 [4–9.2) × 2/d	7.35 (1.52) [5.36–9,17] ×3/d

After dose adjustment from twice to 3 times daily, trough concentrations for 6 patients were in the therapeutic range. Only 1 was under 1 mg/L.
Conclusion: In this population of patients, recommended twice daily dose of 6 mg/kg for the first 24 hours followed by 4 mg/kg cannot lead to trough concentration of 1 mg/L. This adjustment from twice daily to 3 times daily could be a good method to reach the therapeutic range. Nonetheless, more studies should be planed concerning efficacy and tolerance. These data illustrate also the nonlinear pharmacokinetic of voriconazole: from 6.5 mg/kg × 2 per day to 7.4 mg/kg × 3 per day, trough concentrations display a 10-fold increase.
Disclosure of Interest: None declared.

PP196—ENANTIOSELECTIVE METABOLISM OF VENLAFAXINE IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH PSORIASIS

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Introduction: Psoriasis is a common chronic inflammatory skin disease, which has long been recognized to be associated with depression, among other comorbidities. Venlafaxine (VLX), a racemic mixture of (S)-(+) and (R)-(-) enantiomers indicated for the treatment of depressive illness, is metabolized to O-desmethylvenlafaxine (ODV), N-desmethylvenlafaxine (NDV) and N,O-didesmethylvenlafaxine (NODV). Considering that inflammatory disease states have been associated with down-regulation of drug-metabolizing enzymes and transporters in the liver and considering that in psoriasis many CYP in skin are induced, the present study evaluates the influence of psoriasis on kinetic disposition and metabolism of venlafaxine enantiomers.
Patients (or Materials) and Methods: Patients with psoriasis (n = 12) and healthy volunteers (n = 11) were treated with a single oral dose of racemic venlafaxine (150 mg). Serial blood samples were collected up to 48 hours after drug administration. Venlafaxine and its metabolites enantiomers were analyzed in plasma samples by LC-MS/MS coupled with a chiral column Chirobiotic V. Pharmacokinetics parameters were evaluated using the WinNonlin software.
Results: Compared with healthy subjects who were similar overall in terms of age, sex, and body mass index (BMI), the means area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC0-∞) for venlafaxine and its metabolites enantiomers did not differ (unpaired *t* test) in patients with psoriasis. The following